PATENT SPECIFICATION (11) 1 420 946

1 420 946

(21) Application No. 47312/72 (22) Fil d 13 Oct. 1972
(23) Compl t Sp cification filed 12 Oct. 1973
(44) Complete Specification published 14 Jan. 1976
(51) INT CL² A61K 31/085; C11D 10/02, 9/04//(A61K 31/085, 31/13); (C11D 10/02, 1/00, 3/33, 3/48); C11D 9/04, 3/33, 3/48, 9/02)
(52) Index at acceptance
A5E 1A1E 1A1F1 1A1F2 1A1F3 1A1F4 1A1G2 1A1K 1A2B 1A2C 1A2D 1A2F 1A2G 1A2K 1A2N1 1A2N2 1A2N3 1A2N4 1A2P 1A2Y 1A3E 1A3H 1A5A2 1C15B3 1C15D2 1C15D3 1C2D 1C2H 1C8C
A5B 401 40Y 411 41Y 480 482 48Y 586 58Y 642 64Y 771 774
C5D 6A4A 6B11A 6B11C 6B12E 6B12F2 6B12L 6B12N3 6B1 6B2 6B4 6B5 6B6 6C8 6C9

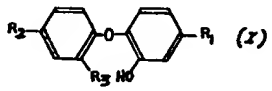
(19)

(54) ANTI-BACTERIAL COMPOSITIONS

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to anti-microbial compositions.

British Patents Nos. 1,022,744 and 1,038,185 and United States Patents Nos. 3,506,720 and 3,642,872 describe inter alia, active anti-microbial agents of the formula (I):



(I)

wherein R_1 is a chlorine or bromine atom; R_2 is a chlorine or bromine atom; and R_3 is a hydrogen, chlorine or bromine atom; and salts thereof.

The compounds of formula (I) were said to have excellent anti-microbial action against many gram positive and gram negative bacteria, and many fungi and to have good skin substantivity. One important gap in the anti-microbial spectrum of the compounds of formula (I) is their lack of useful activity against certain organisms such as *Pseudomonas spp.* and their relatively low activity against certain virulent strains of such organisms as *Aerobactor aerogenes* and *Escherichia coli.* It was suggested in U.S. Patent No. 3,642,872, that mixtures of compounds of formula (I) with other anti-microbial compounds might overcome this disadvantage but no such mixture has yet been reported to give particularly useful activity against *Pseudomonas spp.* unless the added anti-microbial agent had strong anti Pseudomonas activity itself. However, it was demonstrated in British Patent No. 1,090,020, that mixtures of 4,2¹,4¹-trichloro-2-hydroxy diphenyl ether or 4,4¹-dichloro-2-hydroxy diphenyl ether with certain polyhalogenated salicylanilides or polyhalogenated carbanilides did give improved activity against *Escherichia coli* although no increase in activity against *Pseudomonas spp.* was reported.

It has now been found that the overall activity of the compounds of formula (I) against certain more resistant bacterial strains can be increased and the activity against *Pseudomonas spp.* can be vastly increased if the compound is present in conjunction with a certain chelating agent. This is not the first time the addition of chelating agent to an anti-microbial agent has led to an enhancement of activity [see for example, Weiser et al, The Lancet, 1969, (2) 619], but it is believed that no such effect has previously been reported with halogenated hydroxy diphenyl ethers and it is believed the effect reported herein is most unusual in its potency against particularly resistant strains of various organisms and in that, it renders *Pseudomonas spp.* readily susceptible to an agent which when used alone, has no or virtually no anti-*Pseudomonas* activity.

Accordingly, the present invention provides an anti-microbial composition c mprising from 1 to 15 parts f a compound of formula (I) as previously defined together with 3 parts of ethylenediaminetetracetic or a salt thereof, together with a dermatologically or ocularly acceptable carrier.

Ratios used herein are weight/weight ratios. The term EDTA as used herein denotes ethyl nediaminetetracetic acid. Suitable carriers for the active materials may be a solid, liquid which is either pressurised or unpressurised, or gel.

One sub-group of diphenyl ethers of particular usefulness in the composition of this invention are those of formula (I) wherein R_1 and R_2 are chlorine atoms, R_3 is a hydrogen or chlorine atom, and their alkali metal salts.

One compound of formula (I) of particular interest is that wherein R_1, R_2 and R_3 are each chlorine atoms. This compound is currently commercially available in many areas; for example, in the United Kingdom, it is available as IRGASAN DP 300 from Ciba-Geigy Ltd, [IRGASAN is a Registered Trade Mark]. Many details of the possible uses, efficiency, toxicology and suitable formulations of Irgasan DP 300 have been published by and are presently available from Ciba-Geigy Ltd., Basle, Switzerland. Publications on Irgasan DP 300 also include those by Zinkernagle et al, Seifen-Oele-Fette-Waschse, *93*, 670 (1967); Koenig et al, South African Medical Journal, *44*, 848 (1970); Lyman et al, Industrial Medicine and Surgery, 38, 45 (1969); Savage, Drug and Cosm. Ind., *109*, 36 (1971) and in Harry's Cosmeticology, pages 642—643, 6th Ed., 1973, published in London by Leonard Hill Books.

If either active component is present in the form of a salt, it is preferably present as an alkali metal salt, most preferably, as sodium salt. EDTA may be included as its mono-, di-, tri- or tetra basic salt but in general, the di or tri basic salts are preferred. The di- sodium salt of EDTA is particularly useful for inclusion in the anti-microbial compositions.

In the case of 2,4,4^1-trichloro-2^1-hydroxydiphenyl ether, in order to achieve a high order of activity against *Pseudomonas spp.* without needing to use large quantities of the active agents, the ratio of the ether to the chelating agent is advantageously between 2:1 and 1:3, for example, between 2:3 and 1:2.

The compositions of this invention may be presented in forms including those suitable for disinfecting or sanitizing laundry, surgical dressings, skin, floor or other surfaces, plastics, paints and the like, in forms suitable for the prevention of growth of bacteria in cosmetic or toiletry articles or in forms suitable for treating bacterial infections of the eye or skin.

The quantity of the active materials present in such compositions will depend upon the form and intended use of the composition but normally, the compositions of the invention will contain at least 0.02% of a diphenyl ether of formula (I) and at least 0.05% of EDTA. However, such low concentrations of the diphenyl ether component are normally only included if a further anti-bacterial agent such as the previously mentioned salicylanilide or carbanilides are also present.

If the diphenyl ether is the only anti-microbial compound present, then the usual minimum concentration of diphenyl ether present is 0.05% and the usual minimum concentration of EDTA present is 0.1%.

Very high concentrations of the active materials are usually only necessary when the composition of the invention is intended for dilution before use.

The usual highest concentration of diphenyl ether of formula (I) present is 5% and the usual highest concentration of EDTA present is also 5%.

Suitable carriers for the compositions include conventional liquid and solid soaps, deodorant sticks, deodorant creams, cologne, bath additives, shampoos, antiseptic creams or lotions for the skin, eye drops or the like or the carrier may be a solid dispersant such as starch or a solvent such as dilute sodium hydroxide, aqueous ethanol, aqueous acetone or the like.

Carriers for the composition should not contain large (i.e. inactivating) quantities of Lecithin, Tween 80 (Registered Trade Mark for Polyoxyethylene sorbitan mono-oleate) or multi-valent metal ions.

For use in laundry cleansing materials or other sanitizing compositions which are not applied substantively to the skin or are washed from the skin after application, the concentration of ether present is usually in the range 0.2—2%, for example, about 0.4—1%.

For products which are applied substantively to the skin, the concentration of ether present is generally in the range 0.05—0.2%, for example, about 0.1% if it is desired to prevent a high but normal growth of bacteria. In the treatment of infections, higher concentrations may be used, for example, about 2% of ether.

For use in eye infections, compositions containing, for example, up to 1% of the ether and 5% of the chelating agent may be used. However, such composition can cause a reversible but distinct reddening of the conjunctiva at such concentrations so that in general composition for use, the eye does not contain more than about 0.8% of ether. Naturally, compositions for use in the eye should not be noticeably acidic or basic. Such compositions are often made up in gum arabic or other conventional vehicle.

As previously indicated in one of its sanitizing aspects, the present invention provides a composition in the form of a solid or liquid soap or detergent. Such compositions are effective in reducing the bacterial populations of surfaces washed with the composition or a solution thereof. For example, a sanitizing composition of this invention comprising a surface active compound is effective in reducing the populations of gram-positive and gram-negative bacteria including *Pseudomonas spp.*

Another aspect of the subject invention comprises a detergent composition containing a surface active agent and an anti-bacterial composition as disclosed above. Such detergent compositions are effective in reducing the skinflora, both of the gram-positive and gram-negative type, when employed in ordinary washing procedures. As an illustration, detergent compositions comprising a surface active compound and an antibacterial composition of the invention are effective in reducing gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* and gram-negative bacteria such as *Escherichia coli.* Such bacteria are a principal cause of the decomposition of the sebum and perspiration to produce an offensive odour, thus use of the detergent compositions of this invention on the skin can lead to a reduction in body odours..

The surface active agent may be a anionic, nonionic, cationic or amphoteric detergent or a mixture of such detergents.

Among the suitable anionic detergents are water-soluble soaps and conventional sulphated or sulphonated synthetic detergents. The soaps useful in this aspect of the invention are generally water-soluble salts of fatty acids which are usually derived from fats, oils and waxes of animal, vegetable or marine origin, e.g. tallow coconut oil, tall oil and palm kernel oil. Particularly preferred soaps are the sodium and/or potassium salts of coconut oil-tallow mixtures in weight ratios of 10—60 parts of the coconut oil salts to 90—40 parts of the tallow salts.

With respect to the sulphonated synthetic detergents, higher alkyl aryl sulphonates such as an alkyl benzene sulphonate detergent wherein the alkyl group has from 8 to 18 carbon atoms may be used. Suitable examples include sodium decyl benzene sulphonate, sodium dodecyl and pentadecyl sulphonates. Other suitable agents which may be used include surface active water-soluble salts of sulphated or sulphonated aliphatic compounds such as the alkyl sulphonates and sulphuric acid esters of polyhydric alcohols incompletely esterified with higher fatty acids, for example, sodium coconut oil monoglyceride monosulphate, sodium lauryl sulphate, coconut fatty alcohol sulphate, ammonium lauryl alcohol triethoxamer sulphate, sodium coconut fatty acid ethanolamide sulphate and sodium lauric acid amide of taurine. Such anionic surface active agents are normally used in the form of their water-soluble salts, (e.g sodium and potassium salts).

Other suitable anionic detergents include synthetic detergents having a carboylate group and particularly, fatty acid amides of aliphatic amino acid compounds. Typical examples include the water-soluble salts of N-lauroyl or N-cocoyl sarcosine. Other materials are fatty acid amides of polypeptide amino acids.

Suitable ether containing sulphates include lauryl ethyleneoxy sulphates each containing 10 to 18 carbons in the alkyl groups and usually averaging 2 to 6 moles of ethylene oxide.

Nonionic surface active agents include nonionic polyalkylene oxide condensates with an aliphatic or aromatic hydrophobic group. The hydrophobic organic group contains usually from 8 to 30 carbon atoms condensed with at least 5 and usually up to 50 alkylene oxide groups. Examples are polyethylene oxide condensates with alkyl phenols having 6 to 20 carbons in the alkyl group, polythene oxide esters with fatty acids such as tall oil acids or lauric acid condensed with 16 to 20 ethylene oxide groups, polyethylene oxide condensates with aliphatic alcohols, such as lauryl, myristyl or stearyl alcohol with 6 to 30 moles ethylene oxide; polyethylene oxide condensates with fatty acid amides such as coconut fatty acid amide containing 10 to 50 moles ethylene oxide. Water-soluble

polyoxythylene condensates with hydrophobic p lyoxypropylene glycols may be employed als .

Cationic detergents wherein a quaternary nitrogen is part of an open chain or heterocyclic structure may also be used al n or in c mbination with other c mpatible detergents. Examples include lauroyl pyridinium bromide, N(lauroyl colamino formylmethyl) pyridinium chl ride, cetyl trimethyl ammonium chl ride, cetyl pyridinium chloride, stearyl or oleyl, dimethylbenzyl ammonium chloride, stearyl amine acetate and stearyl dimethyl amine hydrochloride.

Other suitable surface active agents which can, under certain conditions, have a cationic nature and which may be used and include alkyl amine oxides such as lauryl dimethyl amine oxides.

Any of the usual amphoteric (ampholytic) detersive materials may also be employed. Among these are alkyl imidazolines such as 1-coco-5-hydroxyethyl-5 carboxymethyl imidazoline and the like, alkyl beta-alanines such as dodecyl beta-alanine and the disodium salt of 1-lauryl-cycloimidium-2-ethoxy-ethionic acid-2-ethionic acid and its corresponding 2-lauryl sulphate derivative.

In antibacterial detergent compositions, the mixture of the diphenyl ether with EDTA is present in an amount of from 0.01% to 5% by weight of the detergent compositions, preferably from 1 to 2%.

A suitable product is a soap bar comprising milled and plodded soap chips prepared from 20% sodium coconut oil soap and 80% sodium tallow soap and containing 0.5 to 1.5% by weight of 4,2',4'-trichloro-2-hydroxy diphenyl ether and 0.5 to 1.5% by weight of EDTA or a salt thereof.

The antibacterial compositions of this invention can be included in detergent compositions such as soap bars, spray-dried and granulated solid compositions, synthetic non-soap detergent bars, combination soap-synthetic detergent bars and liquid detergent compositions. They can also be included in pre-surgical scrubbing compositions which are widely employed in the medical field. The latter detergent compositions are usually in liquid form and contain a detergent such as a potassium soap, sorbitan monooleates, sorbitan monooleate poleoxyethylene derivative and the corresponding lauryl derivatives. A triethanolamine lauryl sulphate or a sodium lauryl ether sulphate may also be included but preferably not as the sole detergent.

Various other ingredients can be included in addition to the antibacterial composition and the surface active agent such as inorganic water-soluble builder salts. Among the most common of these compounds are the water-soluble salts, usually alkali metal or ammonium salts, of sulphuric, phosphoric, silicic, carbonic, boric and hydrochloric acids and derivatives thereof. Of the builder salts, the polyphosphates are of greater utility and applicability but sodium and potassium sulphate, sodium carbonate, sodium silicate, sodium bicarbonate, sodium perborate, borax, sodium chloride, sodium phosphates such as disodium hydrogen phosphate, to name only a few, also exercise desirable building activity.

Various other adjuvant ingredients may be added as is found desirable including compatible perfumes, colouring materials, corrosion or tarnish inhibitors, fluorescent brighteners, thickeners, solvents, lubricants, (to promote flowability), foam enhancers and stabilizers, waxes and colloidal materials such as bentonite. These adjuvants are usually present in minor amount, rarely exceeding 20% by weight and often totalling about 5% and are usually incorporated to improve specific aesthetic or performance characteristics. The amount of solvent may be as much as two-thirds of a liquid detergent composition. If desired, the antibacterial composition may be initially dissolved in a suitable solvent before introduction into a detergent system.

In the formulation of the preferred soap bar of the invention, a suitable procedure comprises mixing soap chips with the antibacterial mixtures either in granular or liquid (i.e. dissolved in a solvent) form, plus such adjuvants as are desired, introducing the mixture thus formed into a soap milling apparatus whereby uniform mixing of all ingredients takes place, and thereafter plodding and pressing the mixture to the desired shape in conventional manner.

Formulation details of conventional cosmetic products may be seen in Harry's Cosmeticology hereinbefore mentioned. In general, the mixtures of active ether and EDTA referred to herein, are suitable for preserving such compositions.

The following Examples illustrate the invention:

EXAMPLE 1.

Using a conventional serial dilution technique, the Minimum Inhibitory Concentrations (M.I.Cs.) given in Table 1 were determined against strains of bacteria which for practical purposes were either effectively resistant to 2,4,4¹-trichloro-2¹-hydroxydiphenyl ether or else were considerably less susceptible to it than most other strains of the relevant organism. The EDTA was present as the disodium salt. The MIC values are quoted in μg/ml of the ether. Organisms marked with an asterisk were isolated from clinical practice.

The figures in Table 1 indicate that the activity of 2,4,4¹-trichloro-2¹-hydroxydiphenyl ether against *Pseudomonas aeroginosa* is increased by a factor of over 100 in the presence of EDTA. The increase in activity against the other gram negative bacteria is about 20 fold. This overall increase in activity against the more resistant strains of the gram negative bacteria is surprising in view of Nen et al [Nature, *225*, 5234 (1970)] who reported a lack of synergy between EDTA and antimicrobials in certain resistant Gram negative bacteria.

TABLE I – MIC VALUES

Ratio of Ether and EDTA Present	Pseudomonas Aeroginosa ATCC 9027	Proteus Vulgaris NCTT 4635	Escheresia Coli NCTT 8110	Aerobactor.* Aerogenes	Stapalococcus Aureus ATCC 6538	Streptococcus* Pyrogenes	Streptococcus* Faecalis
1:0	>10,000	100	100	100	10	25	100
5:1	2,500	50	50	50	5	10	50
5:2	1,000	50	25	50	2.5	10	50
5:5	500	10	10	10	1	5	10
5:10	100	5	5	5	0.5	2.5	5
0:1	>5,000	>5,000	>5,000	>5,000	500	500	500

EXAMPLE 2.

Pseudomonas aeroginosa ATCC 9027 was attempted to be grown in conventional Brain-Heart Infusion Medium (for example, as available from Difco or Oxoid) containing various proportions of 2,4,4¹-trichloro-2¹-hydroxydiphenyl

ether and disodium ethylenediamine tetracetic acid. In the following Table, a "+" means that a definite growth of *Pseudomonas* took place after seeding, a "–" means that no growth of *Pseudomonas* took place after seeding and a "±" means the occasional weak growth of *Pseudomonas* took place after seeding.

% Of 2,4,4¹-Trichloro-2¹-Hydroxydiphenyl Ether In Medium

% of di-Na EDTA in Medium	0.1	0.1	0.2	0.3	0.4	0.5	1.0
0.5	+	±	–	–	–	–	–
0.4	+	+	–	–	–	–	–
0.3	+	+	+	±	–	–	–
0.2	+	+	+	+	+	–	–
0.1	+	+	+	+	+	–	–
0.0	+	+	+	+	+	+	+

The above Table indicates that no growth of *Pseudomonas spp* is likely to take place even in the most favourable environments if they contain (a) 0.5% or more of the ether in the presence of 0.1% or more of EDTA, (b) 0.4% or more of the ether in the presence of 0.3% or more of EDTA, (c) 0.2% or more of the ether in the presence of 0.4% or more of EDTA and vice versa. Naturally, in less favourable environments such as bed linen, floor surfaces, toiletries, cosmetics and the like or in environments where *Pseudomonas spp* has to compete with other bacteria considerably lower concentrations of the active material prevent colonisation by *Pseudomonas spp.*

For example, as may be deduced from Example 1 in many environments, the growth of *Pseudomonas spp.* is effectively prevented by the presence of 100 ppm of 2,4,4¹-trichloro-2¹-hydroxydiphenyl ether in the presence of 200 ppm of ethylenediaminetetracetic acid.

EXAMPLE 3.

The following deodorant compositions were formulated by mixing together the various ingredients in conventional manner. The percentages in the left hand column represent particularly suitable quantities. The figures in the right hand columns represent a generally suitable range of concentrations of the various ingredients in such an antibacterial composition.

Castor Oil	5.1 %	2.0 % —	10.0 %
Sodium Hydroxide	0.68%	0.26% —	1.3 %
Alcohol (95% Ethanol)	16.7 %	5.0 % —	30.0 %
Terpineol	7.0 %	3.0 % —	15.0 %
Perfume	0.3 %	0.01% —	1.0 %
2,4,4¹-Trichloro-2¹-hydroxydiphenylether	0.5 %	0.1 % —	1.0 %
EDTA (Di-sodium Salt)	0.5 %	0.05% —	2.5 %
Dye	0.1 %	0.01% —	1.0%
Water to	100 %		

Similar compositions were prepared using 0.2%, 0.5%, 1.0% and 2% of the ether and 0.2%, 0.2%, 0.5% and 3.0% of the salt of EDTA respectively. The tri- and tetra-sodium salts of EDTA give very similar but slightly less beneficial results.

EXAMPLE 4.

The following non-soap based, non-clouding antibact rial composition was prepared by mixing together the various ingredients.

2,4,4¹-Trichloro-2¹-hydroxydiphenylether	0.5%
EDTA (Di-sodium Salt)	0.5%
Perfume	0.3%
Non Ionic Surfactant	1.0%
Dye	0.1%
Alcohol (95% Ethanol)	10.0%
Water to	100 %

Suitable nonionic surfactants which may be used include conventional fatty acid ethanolamides, fatty acid isopropanolamide and fatty acid diethanolamides and conventional polyglycol ethers and esters.

Similar compositions were prepared using 8.0% alcohol and 30.0% alcohol respectively and 0.2% and 25% surfactant respectively.

EXAMPLE 5.

The following water-in-oil antibacterial compositions were prepared by blending together the various ingredients. The percentages in the left hand column represent a particularly suitable quantities. The figures in the righthand columns represent a generally suitable range of concentrations of the various ingredients in such an antibacterial composition.

Mineral Oil	18.0%	5.0% —	25 %
Beeswax	3.0%	1.0% —	10 %
Ethoxylated Lanolin	5.0%	1.0% —	10 %
Borax	0.5%	0.1% —	2.5%
Magnesium Sulphate	0.1%	0.1% —	0.4%
Perfume	0.5%	0.1% —	2.0%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.5%	0.1% —	2.0%
EDTA (Di-Sodium Salt)	0.5%	0.3% —	5.0%
Water to	100 %		

Similar compositions to those in the left hand above column were prepared containing 0.1%, 0.5%, 1% and 2.0% of the ether and 0.1%, 0.7%, 1.8% and 2.5% of EDTA di-sodium salt respectively. It should be noted that the minimum recommended amount of EDTA in this type of composition is somewhat higher than compositions of Examples 3, 4, 6, 7 or 8 because of the presence of the magnesium ions.

EXAMPLE 6.

The following oil-in-water compositions were prepared by blending togeth r th various ingredi nts. The percentages in the left hand c lumn represent particularly suitable quantities. The figures in th right hand columns represent a generally suitable range of concentration of the various ingredients in such an antibacterial composition.

2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.7%	0.2% —	2.0%
EDTA (As Tri-Sodium Salt)	1.5%	0.2% —	2.0%
Stearic Acid	3.0%	1.0% —	10.0%
Propylene Glycol Mono Stearate	1.0%	0.2% —	2.5%
Mineral Oil	4.0%	2.0% —	10.0%
Glycerin	2.5%	1.0% —	5.0%
Sodium Carboxymethyl Cellulose	0.3%	0.1% —	0.5%
Triethanolamine	1.0%	0.3% —	1.7%
Perfume	0.5%	1.0% —	1.0%
Water	100 %		

EXAMPLE 7.

The following especially suitable antibacterial composition was prepared by blending together, the various ingredients.

Stearic Acid	3.0%
Propylene Glycol Mono Stearate	1.0%
Polawax	0.5%
Mineral Oil	4.0%
Glycerin	2.5%
Carbopol 934	0.5%
Triethanolamine	1.0%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.5%
EDTA (As Di-Sodium Salt)	0.5%
Perfume	0.5%
Water to	100 %

Carbopol 934 (Registered Trade Mark) is high grade carboxypolymethylene and may be supplied by, for example, Goodrich Chemical Co. Polawax (Registered Trade Mark) is a waxy solid, prepared from cetostearyl alcohol and containing a polyoxyethylene derivative of a fatty acid ester of sorbitol and may be supplied by, for example, Croda.

EXAMPLE 8.

The following aerosol formulation was prepared by blending and filling in conventi nal manner —

2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.08%
EDTA (Di-Sodium Salt)	0.08%
Dichlorophen	0.25%
Perfume	1.25%
Alcohol Denaturant	0.01%
Diethylphthalate	1.39%
Propellant	10.00%
Ethanol to	100 %

Propellants which may be used include trichloromonofluoromethane, dichlorofluoromethane and dichlorotetrafluoroethane.

EXAMPLE 9.

The following skin cream was prepared by blending the ingredients in conventional manner.

Stearic Acid	15.0%
Cetyl Alcohol	0.5%
Sodium Hydroxide	0.4%
Triethanolamine	1.2%
Isopropyl myristate	3.0%
Glycerine	6.0%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.1%
EDTA (Di-Sodium Salt)	0.2%
Perfume	0.1%
Water to	100 %

Similar preparations were prepared using 0.3 and 0.5% of ether and 0.1 and 0.8% of EDTA respectively.

EXAMPLE 10.

The following mild astringent skin lotion was prepared by blending t gether the vari us ingredi nts.

Glycerin	5.0%
Ros Water	15.0%
Alcohol (95%)	30.0%
Menthol	0.2%
EDTA (Di-Sodium Salt)	0.2%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.2%
Water to	100 %

EXAMPLE 11.

The following body powders were prepared by pulverising the ingredients, sieving, blending, repulverising and resieving —

	A	B	C
Oracid	65 %	60 %	—
Rice Starch	30 %	20 %	82 %
Avicel	—	10 %	10 %
Sodium Stearate	4 %	6 %	5 %
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.2%	0.2%	0.5%
EDTA (Di-Sodium Salt)	0.3%	1.0%	1.9%
Perfume and Colour to		100%	

Oracid (Registered Trade Mark) is a micronized rigid urea formaldehyde foam. Avicel (Registered Trade Mark) is a micro-crystalline cellulose.

The average particle size of the ingredients was in the range 1—10 microns, generally, about 6 microns.

It should be noted that the body powders have avoided using large quantities of magnesium or calcium salts. At one time, powders comprising large proportions of starch were in wide use but objections were raised to the use of starch because when moist, it is an ideal nutrient for bacteria. Naturally, in the present compositions such a defect cannot arise because of the excellent antibacterial properties of the composition.

EXAMPLE 12.

The following lipstick showed no tend ncy to all w bact rial growth —

Isopropyl Myristat	1.7%
Halogenated Fluoresceins (Dy s)	6.0%
Hardened Castor Oil	22.0%
Stearic Acid	2.0%
Stearyl Alcohol	8.0%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.2%
EDTA (Di-Sodium Salt)	0.1%
Hexadecyl Alcohol	50.0%
Carnauba Wax	10.0%

The lipstick was prepared by blending together the oily materials, blending together the dyes and the preservatives and then combining the two sets of materials and warm blending the mixture in a conventional colloid mill.

EXAMPLE 13.

A barrier cream comprising —

a) Stearic Acid	6.0%
b) Cetyl Alcohol	4.0%
c) Lanolin	4.0%
d) Petroleum Jelly	1.0%
e) Sodium Hydroxide	1.0%
f) EDTA	0.5%
g) 2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.2%
h) Avicel	20.0%
i) Water to	100.0%

was prepared by warming together (a), (b), (c) and (d) at 70°C, warming together (e), (f), (g) and (i) at 75°C and then blending the two mixtures together; when the material had cooled to 40% the Avicel was added and the mixture homogenized.

EXAMPLE 14.

Th following bath oil was prepared by blending —

Lauric Di thanolamide	5.0%
Monoethanaolamin Lauryl Ether Sulphate	20.0%
Hexylene Glycol	5.0%
Lauric Ethanolamide	10.0%
Ethanol	10.0%
Ethoxylated Coconut Monoethanolamide	5.0%
Glycerin	5.0%
Perfume and Colour	0.1%
Sodium Hydroxide	0.4%
EDTA (Di-Sodium Salt)	7.5%
2,4,4^1-Trichloro-2^1-hydroxydiphenyl ether	2.5%
Water to	100.0%

EXAMPLE 15.

The following shampoo was prepared by blending —

Polyoxyethylene Sorbitan Monolaurate	10.0%
Sorbitan Mono-oleate	20.0%
Triethanolamine Lauryl Sulphate	10.0%
Coconut Diethanolamide	5.0%
2,4,4^1-Trichloro-2^1-hydroxydiphenyl ether	0.1%
EDTA (Di-Sodium Salt)	0.4%
Sodium Carbonate	0.5%
Glycerine	1.0%
Colour and Perfume	q.s.
Water to	100.0%

EXAMPLE 16.

The following hair conditioner was prepared by blending —

EDTA (Di-Sodium Salt)	0.3%
Stearyl Alcohol	1.0%
Cetyl Alcohol	2.0%
Glycerol Monostearate	1.0%
Alcohol (Perfumery Quality)	45.0%
Perfume and Colour	q.s.
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.1%
Water to	100.0%

EXAMPLE 17.

The following baby powders were prepared by milling the dry micronized materials —

Sterilized Starch	92.7%
Stearic Acid	2.0%
Stearic Acid Sodium Salt	2.0%
Cetyl Alcohol	2.0%
EDTA (Di-Sodium Salt)	1.0%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.3%
Perfume	q.s.

EXAMPLE 18.

The following baby oil was prepared by blending together at 35°C —

Light Mineral Oil	35.0%
Lanolin	1.0%
Cetyl Alcohol	1.0%
EDTA (Di-Sodium Salt)	0.5%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.2%
Sorbitan Mono-oleate	8.0%
Triethanolamine	1.0%
Perfume	q.s.
Water to	100.0%

EXAMPLE 19.

The following shaving soap —

Stearic Acid	35.0%
Coconut Oil	10.0%
Potassium Hydroxide	7.0%
Sodium Hydroxide	1.5%
Glycerine	10.0%
EDTA (Di-Sodium Salt)	0.3%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.1%
Perfume	q.s.
Water to	100.0%

was prepared by mixing half the stearic acid with the coconut oil and warming to 70° (mixture melts) and then adding a mixture of the other ingredients. The mixture was stirred until saponification was complete and then blended with the remaining stearic acid.

EXAMPLE 20.

A bar soap capable of producing a major reduction in skin bacteria when used was prepared by thoroughly blending 96% of conventional ivory soap with 2.5% of di-sodium EDTA and 1.5% of 2,4,4¹-trichloro-2¹-hydroxydiphenyl ether.

Similar soaps were prepared containing 2% and 1% of di-sodium EDTA and 2% and 0.4% of the ether respectively.

EXAMPLE 21.

A liquid toilet sanitizing composition was prepared containing —

EDTA	12.0%
2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	6.0%
Sodium Perborate	1.0%
Methyl Cellulose 450 (B.P.) (optional)	1.0%
0.5 N Sodium Hydroxide Solution to	100.0%

EXAMPLE 22.

The following antiseptic creams may be prepared —

	A(%)	B(%)	C(%)
Lanolin	15.0	30.0	20.0
Soft Paraffin	15.0	15.0	30.0
Beeswax	10.0	5.0	—
Propylene Glycol	—	5.0	2.0
Stearyl Alcohol	10.0	110.0	5.0
Isopropyl Myristate	—	2.0	—
Borax	0.3	0.1	—
Di-Sodium EDTA	0.4	0.3	0.2
2,4,4^1-Trichloro-2^1-hydroxydiphenyl ether	0.2	0.1	0.2
Zinc Oxide	—	10.0	8.0
Arachis Oil	15.0	—	6.0
Sorbitan Monolaurate	0.5	1.0	—
Water	to 100.0	to 100.0	to 100.0

Cream B may be used for the treatment of Napkin rash and Cream C may be used for the treatment of minor burns. Cream A may be used for the treatment of infected skin.

EXAMPLE 23.

The following antiseptic lotions may be prepared.

	A(%)	B(%)	C(%)
2,4,4^1-Trichloro-2^1-hydroxydiphenyl ether	0.1	0.3	0.5
Di-Sodium EDTA	0.2	0.8	0.5
Ethanol	25.0	20.0	35.0
Potassium Hydroxide	0.5	0.5	0.5
Terpineol	5.0	0.0	0.0
Water	to 100.0	to 100.0	to 100.0

EXAMPLE 24.

The following mixture —

2,4,4¹-Trichloro-2¹-hydroxydiph nyl ether	2.0%
Di-sodium EDTA	2.0%
Ethanol	54.0%
Sorbitan Mono-oleate	2.0%
Sodium Hydroxide	2.0%
Water to	100.0%

may be diluted with twice its volume of water for pre-operative skin disinfection or used neat or with an equal volume of water for sterilizing surgical instruments.

EXAMPLE 25.

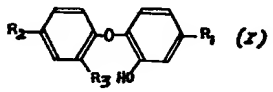
An eye ointment may be prepared by blending together and sterilizing at 160°C for one hour the following —

Micronized 2,4,4¹-Trichloro-2¹-hydroxydiphenyl ether	0.1%
Micronized Di-Sodium EDTA	0.3%
Water	2.0%
Liquid Paraffin	10.0%
Lanolin	20.0%
Yellow Soft Paraffin to	100.0%

Such an ointment will not permit the growth of *Psuedomonas spp.* in stock supplies and so cannot transfer *Pseudomonas* to the eye as has been reported with certain other eye preparations.

WHAT WE CLAIM IS:—

1. An anti-microbial composition comprising from 1 to 15 parts of a compound of formula (I):



wherein R_1 is a chlorine or bromine atom, R_2 is a chlorine or bromine atom and R_3 is a hydrogen, chlorine or bromine atom or a salt thereof and 3 parts of ethylenediaminetetracetic acid or a salt thereof, together with a dermatologically or ocularly acceptable carrier, other than lecithin, polyoxyethylene sorbitan monooleate or multi-valent metal ions in inactivating quantities.

2. A composition as claimed in Claim 1 wherein R_1 and R_2 are chlorine atoms and R_3 is a hydrogen or chlorine atom.

3. A composition as claimed in Claim 1 or Claim 2 wherein R_1, R_2 and R_3 are chlorine atoms.

4. A composition as claimed in any one of Claims 1—3 wherein the carrier is a solid, liquid, which is either pressurised or unpressurised, or gel.

5. A composition as claimed in any one of Claims 1—4 wherein the ethylenediaminetetracetic acid is in the form of an alkali metal salt.

6. A composition as claimed in Claim 5 wherein the salt is the di- or tri-sodium salt.

7. A composition as claimed in any one of Claims 3—6 wherein the ratio of 2,4,4¹-trichloro-2¹-hydroxydiphenyl ether or salt thereof to EDTA or salt thereof is between 2:1 and 1:3.

8. A comp sition as claimed in Claim 7 wherein the rati of ether to EDTA is from 2:3 to 1:2.

9. A composition as claimed in any one of Claims 1—3 in a form n t generally applied substantively to the skin, which comprises 0.2—2% of a compound of formula (I).

10. A composition as in Claim 9 in a form not generally applied substantively to th skin which comprises 0.4—1% of 2,4,4¹-trichloro-2¹-hydroxydiphenyl ether.

11. A compositi n as claimed in any one f Claims 1—3 in a form suitable for applying substantively to the skin which comprises 0.05—0.2% of a compound of formula (I).

12. A composition as claimed in Claim 11 in a form suitable for applying substantively to the skin, which comprises 0.05—0.2% of 2,4,4¹-trichloro-2¹-hydroxyphenyl ether.

13. A composition as claimed in Claim 1, substantially as described hereinbefore in any one of Examples 3 to 25.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1976.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.